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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/616,203	07/08/2003	Kathleen D. Danenberg	7000613003	5971

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FITCH EVEN TABIN AND FLANNERY
120 SOUTH LA SALLE STREET
SUITE 1600
CHICAGO, IL 60603-3406

EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 10/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/616,203	DANENBERG ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' preliminary amendment filed on 12/24/2003 is acknowledged and has been entered. Claims 1-17 have been cancelled. Claims 18-49 have been added and are pending in the instant application.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-25, 28, 30-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanta et al (Biotechnique, vol. 24, pages 271-276, February 1998) and Stanta et al (Methods in Molecular Biology: RNA Isolation and characterization protocols, Humana Press, Inc, Totowa, NJ, pages 23-26, 1998) and further in view of Koopmans et al (Journal of Virological Methods, Vol. 43, pages 189-204, 1998). Regarding claims 18, 42, 45 and 46, Stanta et al teach a method for quantitative measurement of gene expression of a target RNA in a fixed paraffin embedded

tissue sample, comprising: (a) deparaffinizing the tissue sample to obtain a deparaffinized sample; (b) isolating mRNA from the sample by first heating the tissue sample in a Proteinase K solution at 45°C overnight (see Stanta, Methods in Molecule Biology for exaction protocol of RNA, page 25-25); (c) subjecting the isolated mRNA to amplification using a pair of oligonucleotide primers capable of amplifying a region of the target mRNA gene, to obtain an amplified samples; and determining the quantity of target gene mRNA relative to the quantity of an internal control gene's mRNA from the isolated mRNA (see entire reference, pages 272-276). Stanta et al differs from the instant invention in that the reference does not teach wherein the mRNA is isolated from the deparaffinized sample by heating the tissue sample in a chaotropic solution comprising an effective concentration of a chaotropic agent to a temperature in the range of about 50 to about 100°C for a time period of about 5 to about 120 minutes.

Koopsman et al teach a method of recovering RNA from formalin-fixed paraffin embedded biological sample comprising deparaffinizing the sample, isolating mRNA from the deparaffinized sample by first heating the tissue sample in a chaotropic solution comprising an effective concentration of a chaotropic agent to a temperature of about 50°C for a time period of about 30 minutes and recovering the mRNA from the chaotropic solution to yield isolated mRNA and subjecting the mRNA to amplification using a pair of oligonucleotide primers and determining the quality and quantity of RNA by spectrophotometry (page 193-195 and 201). Koopsman et al compares the chaotropic solution mRNA extraction method with mRNA extraction using proteinase K solution. Koopsman et al concludes that mRNA extraction with either a chaotropic solution or proteinase K solution results in amplifiable RNA when sufficient template is used for the amplification reaction by PCR. Therefore, one of ordinary skill in the

art at the time of the claimed invention would have been motivated to have modify the RNA quantitative analysis method of Stanta et al and Stanta et al to encompass mRNA extraction using a chaotropic solution rather than proteinase K solution with a reasonable expectation of success based on the teachings of Koopsman et al that the use of either extraction method results in amplifiable RNA and is capable of being quantitatively analyzed (Koopsman, page 201).

Regarding claims 19 and 20, Koopsman et al teach the method of claim 18, further comprising rehydrating and homogenizing the sample before heating (page 193, beginning at "RNA extraction" to page 195).

Regarding claims 21-23, Koopsman et al teach the method of claim 18, wherein the isolated RNA is recovered with a water insoluble solvent comprising chloroform and purifying the RNA using ethanol precipitation (page 193, beginning at "RNA extraction" to page 195).

Regarding claim 24, 25, Koopsman et al teach the method of claim 18, wherein the time period of the heating about 30 minutes (page 193, beginning at "RNA extraction" to page 195).

Regarding claim 28 and 30, Koopsman et al teach the method of claim 18, wherein said chaotropic agent is a guanidinium compound, such as guanidinium isothiocyanate (page 193).

Regarding claim 31, Koopsman et al teach the method of claim 30, wherein said guanidinium isothiocyanate is present at a concentration of 4.7 M (page 193).

Regarding claim 32, Koopsman et al teach the method of claim 30, wherein said guanidinium isothiocyanate is present at a concentration of about 4 M (page 193).

Regarding claims 33 and 34, Koopsman et al teach the method of claim 28, wherein said chaotropic solution has a pH of about 4 or about 6 (page 193).

Regarding claim 35-37, Koopsman et al teach a method according to claim 18, wherein said chaotropic solution further comprising a reducing agent, wherein said reducing agent is dithiothreitol or beta-mercaptoethanol (page 193).

Regarding claim 38, Koopsman et al teach a method according to claim 18, wherein the tissue sample is formalin-fixed and paraffin embedded (FFPE) (page 193).

Regarding claim 39, 44 and 47, Stanta et al teach a method for according to claim 18, wherein determining the relative gene expression level is determined using RT-PCR (Abstract and full reference).

Regarding claim 40, Stanta et al teach the method of claim 18, wherein the relative quantity of target gene mRNA in said tissue sample is the same whether said tissue sample is formalin-fixed and paraffin embedded or frozen (see entire reference).

Regarding claim 41, Stanta et al teach the method of claim 18, wherein the internal control gene is beta-actin (page 175).

Regarding claims 48 and 49, Koopsman et al teach the method of claim 18, wherein the mRNA is isolated free of DNA present in the sample ((page 193, beginning at "RNA extraction" to page 195).

5. Claims 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanta et al and Stanta et al in view of Koopsman et al as previously applied above and further in view of Miyauchi et al (Pathology International, vol. 48, pages 428-432, 1998). Regarding claim 26 and 27, Stanta et al and Stanta et al in view of Koopsman et al teach a method of quantitative measurement of gene expression of a target gene in a fixed paraffin embedded tissue sample as

previously described above. The references differs from the instant invention in that they do not teach wherein the isolation of mRNA in a chaotropic solution occurs at a temperature in the range of about 85 to about 100°C for a time period of about 30 to 60 minutes.

Miyauchi et al teach a method comprising the steps of deparaffinizing a formalin-fixed paraffin-embedded biological tissue sample, comprising the deparaffinizing section with a chaotropic solution having a pH of about 6 and comprising guanidinium thiocyanate at a concentration about 5 M, heating the sample and the chaotropic solution to temperature of about 100°C for about 30 minutes and recovering the sample's RNA (page 429, col. 1, lines `0-`6 and col. 2, lines 1-3). Miyauchi et al teach that this extraction method is useful for extraction of viral RNA from formalin-fixed paraffin-embedded liver tissues for subsequent analysis (see page 432). In view of the teachings of Miyauchi et al, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention that higher temperatures may be used in the quantitative RNA analysis method of Stanta et al and Stanta et al in view of Koopsman et al based on the practitioner's desired RNA target to be isolated.

6. Claims 29-34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stanta et al and Stanta et al in view of Koopsman et al as previously applied above and further in view of Chomcynski (5,346,994, September 1994). Regarding claims 29 and 30, Stanta et al and Stanta et al in view of Koopsman et al teach a method for quantitative measurement of gene expression of a target gene in a fixed paraffin embedded tissue sample as previously described above. The references do not teach wherein the method comprises isolating mRNA from the deparaffinized

sampled by first heating the tissue in a chaotropic solution comprising guanidinium hydrochloride.

Chomczynski teaches a method of DNA, RNA or protein extraction from a biological sample, the method comprising incubating the sample in a chaotropic solution comprising a guanidinium compound, wherein the guanidinium compound is guanidinium hydrochloride or guanidinium thiocyanate (col. 3, lines 1-4). Chomczynski et al teach that these chaotropic compounds protect the RNA or DNA from degradation (col. 3, lines 4-8). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention to have been motivated to have use guanidinium hydrochloride or guanidinium thiocyanate as the guanidinium compound in the chaotropic solution with a reasonable expectation of success for the benefit of protecting the RNA or DNA from degradation as taught by Chomczynski. Additionally, different guanidinium compounds are routinely used in methods of extraction or isolation of DNA or RNA.

Regarding claim 31 and 32, Chomczynski teaches the method of claim 28, wherein the concentration of the guanidinium compound is in the range of 2-5M (col. 2, lines 50-51).

Regarding claim 33 and 34, Chomczynski teaches the method of claim 28, wherein the ph of the chaotropic solution is in the range of about 4 to 6 (col. 3, lines 19-20).

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 18-23, 28, 30, 37, 42 and 45 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6613518 B2.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant invention only differs from the claims 1-6 of US patent 6613518 in that the claims of the US patent 6613518 are narrower in scope and does not encompass the broad range of heating temperature and time period for the sample in the chaotropic solution as that of the instant invention. However, the claims 18-23, 28, 30, 37, 42 and 45 encompass the temperature and time period of heating of the chaotropic solution as recited in the claims 1-6 of US patent 6613518. Likewise the claims of the instant invention do not recite wherein the amplification is by PCR in a reaction that comprises a polymerase and a fluorochrome. However, the

specification for the instant application defines that the amplification reaction is by real-time PCR based on fluorescent detection methods. Such methods encompass a PCR in the presence of a polymerase and fluorochrome.

Thus, the claims 1-6 of US Patent 6613518 falls entirely within the scope of the claims 18-23, 28, 30, 37, 42 and 45 of the instant application.. As the court stated in *In re Goodman*, 29 USPQ2d 2010 (CAFC 1993), " a second application-- "containing a *broader claim*, more generical in its character than the specific claim in the prior patent"--typically cannot support an independent valid patent. Miller, 151, U.S. at 198; See Stanley, 214 F.2d at 153. Thus, the generic invention, as noted above is "anticipated" by the species of the patented invention. Cf., Titanium metal corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (holding that an earlier species disclosure in the prior art defeats any generic claims). This court's predecessor has held that, without a terminal disclaimer, the species claims preclude issuance of the generical application. "*In re Van Ornum*, 686 F.2d 937, 944, 214 USPQ 761, 767 (CCPA 1982); *Schneller*, 397 F.2d at 354".

Conclusion

9. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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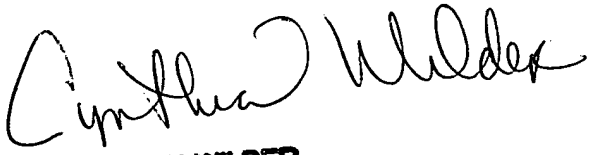

CYNTHIA WILDER
PATENT EXAMINER

9/30/2005